IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	Confirmation No.: 6830
Jane HIRSH	)	Group Art Unit: 1618
Application Number: 10/690,872	)	Examiner: Leah H. Schlientz
Filed: October 22, 2003	)	
For: PULSATILE RELEASE COMPOSITIONS OF MILNACIPRAN	)	

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Dear Sir:

Applicants request a pre-appeal conference in the above-identified application. A Notice of Appeal is filed concurrently herewith.

The following responds to the Final Office Action mailed August 12, 2009 ("Office Action"), rejecting the pending claims under 35 U.S.C. § 103(a) over various combinations of the following references: (1) U.S. Patent No. 6,340,476 to Midha *et al.*; (2) Marc Ansseau *et al.*, 114 *Psychopharmacology* 131-137 (1994); (3) U.S. Patent No. 6,699,506 to Paillard *et al.*; (4) Published U.S. Appl. No. 2003/0203055 to Rao *et al.*; (5) Neliat *et al.*, 35 *Neuropharmacology* 589, 592 (1996); (6) U.S. Patent No. 6,228,398 to Devane *et al.*; and (7) U.S. Patent No. 7,008,640 to Watanabe *et al.*

I. *Introduction*

Claim 1 is directed to a formulation that provides pulsatile release of milnacipran. The formulation comprises an immediate release solid dosage unit comprising a first dose of milnacipran and a delayed release solid dosage unit comprising a delayed release polymer and a second dose of milnacipran. There is a lag time between the release of milnacipran from each solid dosage unit where substantially no milnacipran is released. The formulation produces a therapeutic effect over 24 hours with diminished incidence or reduced intensity of side effects.

Claim 1 recites two separate releases of milnacipran, the first occurring immediately and the second occurring 3 to 10 hours following oral administration of the formulation. The claim also provides that, following the first release, there results "a first plasma level peak at a time between approximately 0.05 hours to less than approximately 3 hours." This language reflects the fact that although the drug is released from the immediate release solid dosage unit immediately upon ingestion, absorption of the drug (*i.e.*, transfer from the GI tract into the circulatory system) occurs over a period of time following release. Although not explicitly recited, there is likewise an absorption timeframe following the second release at 3 to 10 hours, wherein the drug is present in the GI tract and available for absorption, which occurs over a period of five or more hours.[1]

Indeed, for reasons discussed in detail below, even when the second release of milnacipran occurs early in the claimed range (*i.e.*, near three hours), a therapeutically significant amount of the drug will still absorb while it is in the colonic region of a patient, corresponding to five or more hours. Accordingly, in reciting a 3 to 10 hour release of the second dose of milnacipran, the claim necessarily requires that a significant amount of the drug be absorbed colonically.

II. *The Combination Of References Does Not Render The Claims Obvious*

It is well known that lipo**philic** drugs absorb well in the colon, whereas lipo**phobic** drugs (*e.g.*, polar drugs) do not. *See, e.g.*, S. A. Riley *et al.*, *Aliment. Pharmacol. Ther. 6*: 701-706 (1992). Indeed, this fact has played prominently in a Federal Circuit decision involving a controlled release drug. *See Alza Corp. v. Mylan Labs., Inc.* 80 U.S.P.Q.2d 1001 (Fed. Cir. 2006). Additionally, because lipophilic drugs are generally amenable to colonic absorption, they are generally suitable for use in pulsatile-release systems for the simple reason that typically, by the second or third pulse, the drug will have travelled to the colonic region where efficacy depends on the ability of the colon to absorb that drug. It will further come as no surprise that the opposite is true of highly hydrophilic drugs such as milnacipran. That is, because hydrophilic

[1] The absorption period following the first release of milnacipran is shorter than the absorption period following the second release. Two factors may contribute to the observed difference: (1) the dosage form may disintegrate faster in the stomach than in lower regions of the GI tract where less water is available to dissolve the formulation; and (2) the drug likely absorbs faster in the upper regions of the GI tract than in the lower small intestine and colon due to the relative rates of drug permeation in these regions. (Fagerholm, *Journal of Pharmacy and Pharmacology 59*:905-916 (2007)).

drugs generally do not absorb well in the colonic region, those of skill in the art would not be motivated to use pulsatile controlled-release drug delivery technology with hydrophilic drugs. This is because, by the second or third pulse, the drug is released in a region where one would not expect the drug to be sufficiently absorbed. All of the prior art relied upon by the Patent Office is consistent with this observation. Midha, the primary reference on which all of the present rejections depend, teaches formulations that release methylphenidate, a lipophilic drug, in a pulsatile fashion. Devane, like Midha, also teaches formulations that release methylphenidate in a pulsatile fashion.

In addition to being lipophilic, the drugs cited in the prior art appear to have short half-lives. It is highly desirable to deliver drugs with short half-lives in a pulsatile fashion in order to maintain therapeutic levels of the drug *in vivo*. In the Declaration of Alison B. Fleming Under 37 C.F.R. § 1.132 filed on May 13, 2009 ("the Declaration"), Applicants' expert, Dr. Alison Fleming, confirms that drugs with short half-lives (*e.g.*, less than three hours) are well-suited for pulsatile release. And, because the drugs cited in the prior art also happen to be lipophilic, it won't matter that the second and/or third pulses are delivered in the colonic region of the GI tract. This is because such liphophilic compounds will absorb well in the lower regions of the GI tract.

Midha and Devane disclose the use of methylphenidate.[2] Methylphenidate has a half-life in the order of 2 hours, which is considered short. *See* http://www.mentalhealth.com/drug/p30-r03.html (last visited May 12, 2009). Accordingly, methylphenidate is well-suited for pulsatile release. And, as Dr. Fleming explains, because methylphenidate is a ***lipophilic*** drug, it won't matter that a second pulse of the drug would be delivered in the colonic region of the GI tract. This is because such a liphophilic compound will absorb well in the lower regions of the GI tract.. Declaration of Alison B. Fleming Under 37 C.F.R. § 1.132, at page 6. *See* also http://uuhsc.utah.edu/pharmacy/bulletins/NDB_112.pdf

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[2] Other drugs discussed in the art cited by the Office include ketoprofen and ibuprofen. *See* Devane 2:41-45. Ketoprofen and ibuprofen also have short half lives (1-3 hours and 1.8-2 hours, respectively). *See* http://www.healthcareprescriptiondrugabuse.com/Ibuprofen.html (last visited May 12, 2009). Accordingly, it would be desirable to administer such drugs in a pulsatile fashion. In addition, ketoprofen and ibuprofen are lipophilic. *See* T. Ngawhirunpat *et al.*, *Pharmazie 56*: 231-234 (2001) (for ketoprofen); and F.R. Formiga *et al.*, *Int'l J. of Pharmaceutics 344*: 158-160 (2007) (for ibuprofen).

By contrast, milnacipran has a significantly longer half-life than the drugs cited in the prior art.[3] Because milnacipran has a longer half-life, the skilled artisan would not have been motivated to deliver milnacipran in a pulsatile format. Typically, an extended release formulation would be considered to maintain therapeutic blood levels over a longer time period than can be achieved with an immediate release dosage form. Contrary to conventional wisdom, in the present invention, it was recognized that a pulsatile system could provide the advantages of delivering a drug in a divided dose, with a reduction in side effects, while providing a once-a-day formulation. In addition, because milnacipran is highly hydrophilic/lipophobic, one of ordinary skill would not have been motivated to deliver a second or more pulses of the drug in the lower regions of the GI tract. This is because one of skill in the art would not have predicted that compounds like milnacipran would be effectively colonically absorbed. Indeed, the inventors' disclosure that a substantial amount of the milnacipran is absorbed efficiently in the colon was surprising.

In sum, the prior art, including Midha and Devane, does not provide the requisite motivation to use a highly lipophobic drug, such as milnacipran, in the a pulsatile release system, as claimed. First, given the longer half life of milnacipran, there simply did not exist at the time of the invention the same motivation to provide a pulsatile release of such a long half life drug. Second, one of ordinary skill in the art would not have even believed it feasible to employ a pulsatile release system as claimed with milnacipran because it would not have been expected to be absorbed in the colonic region where release occurs according to the claim.

III. *Paillard discourages the slow release of milnacipran*

Paillard teaches multiparticulate, ***extended release*** milnacipran formulations. Paillard makes no mention of ***delayed release*** milnacipran formulations. Further, a close reading of the reference reveals that it actually discourages the skilled artisan from releasing milnacipran slowly from a dosage form. Indeed, all but three of Paillard's formulations release (*in vitro*) between 40 and 75% of the milnacipran in 4 hours.[4]

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[3] Unlike the drugs cited by the Office, which are lipophilic and have relatively short half-lives, milnacipran is highly lipophobic and has a half-life of approximately 8 hours. See ¶ [0012] of Published U.S. Application 2004/0121010.

[4] As for the other three formulations, Paillard characterizes these as "not mak[ing] it possible to achieve the abovementioned objective *in vitro*." *Paillard* at 12:41-45; 14:63-67; 16:34-38, respectively.

Representative *in vitro* dissolution profiles for the claimed milnacipran formulations, by contrast, reveal that less than 10% of the milnacipran is released in 2 hours. *See* Figure 1 of Keller Decl., filed January 3, 2008. In fact, only one of the claimed formulations ("lot #6") releases about 10% in 4 hours. In short, the delayed release solid dosage unit portion of the claimed formulations is significantly different than Paillard's extended release milnacipran formulation.

That Paillard discourages the slow release of milnacipran is consistent with the wisdom at the time the claimed invention was made. As discussed above, one of ordinary skill in the art at that time would have sought to release a highly hydrophilic/lipophobic drug, such as milnacipran, relatively quickly (*e.g.*, 10-55% in the first two hours) because it was well known that such drugs are absorbed best in the upper GI tract. Accordingly, rather than render the claimed formulations obvious, Paillard actually teaches away from them.

Applicants respectfully submit that the Applicants respectfully submit that the 35 U.S.C. § 103 rejections over the art of record can not stand for the reasons set forth above. Accordingly, Applicants respectfully request withdrawal of these rejections.

Respectfully submitted,
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Dated: December 14, 2009

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